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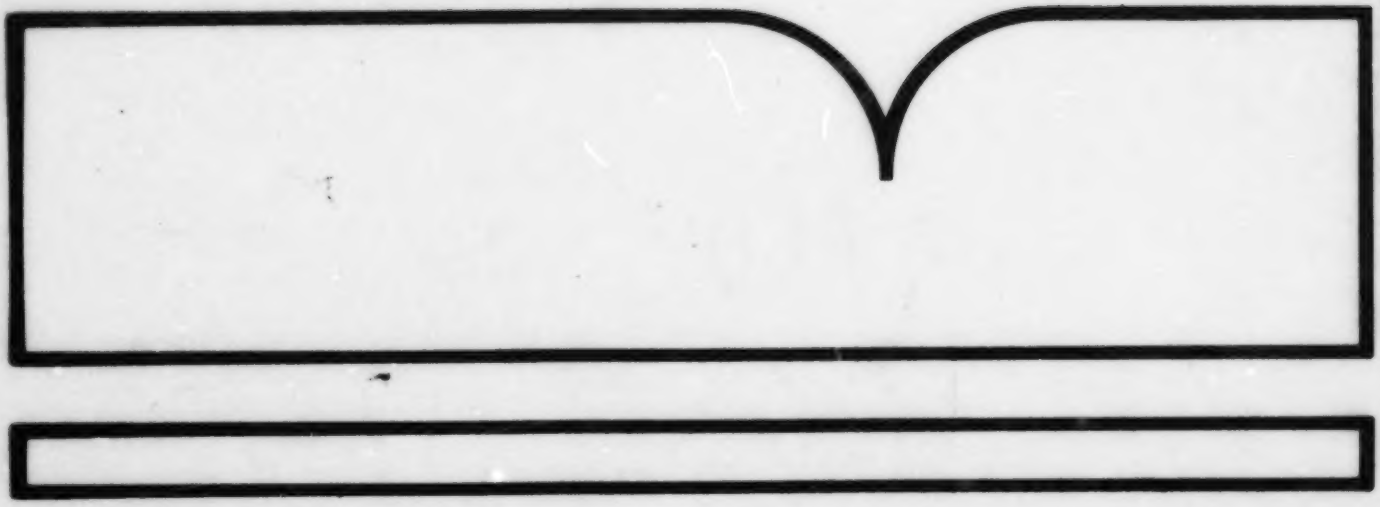

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# Olfaction: Anatomy, Physiology and Behavior

## by Vernon A. Benignus*† and James D. Prah*

**The anatomy, physiology and function of the olfactory system are reviewed, as are the normal effects of olfactory stimulation. It is speculated that olfaction may have important but unobtrusive effects on human behavior.**

The sense of smell has been neglected in comparison to other senses. Among the reasons for this are (a) inaccessibility of anatomical structures, (b) limited theoretical knowledge about the nature of the physical stimulus, (c) difficulty with generating and presenting stimuli and (d) the belief that the olfactory sense is not important to man. Some of these reasons remain problems, but techniques for dealing with them are being devised (*1*). No recent major advance in olfactory stimulus theory has occurred. The belief about the unimportance of olfaction has been questioned recently and is discussed in this paper.

The major reason for reviewing olfaction in a toxicological/environmental context is that this neural tissue is directly exposed to air pollutants. Since these olfactory receptors appear to function by retaining molecules on their surface, airborne pollutants and toxic substances have a high potential for producing olfactory damage. The olfactory system is perhaps the most vulnerable neural tissue in terms of airborne pollutants, since the receptors are: directly exposed and are also exposed via the circulatory system to bloodborne toxicants.

This review describes the anatomy and physiology of the olfactory system and also discusses the behavioral implications of this sense. In the limited space available only overall conclusions can be given. Key references will be cited for further study.

## Olfactory Anatomy

### Peripheral Anatomy and Physiology

***Nasal Passages.*** Peripheral features of the olfactory system are illustrated in Figures 1 and 2. Due to shape of the turbinate bones, only about 2% of inspired air reaches the olfactory epithelium during normal respiration (*4*). During passage over the nasal epithelium, temperature and humidity of inspired air are altered to body temperature and nearly saturation (*5*). Particulate matter in inspired air is deposited on nasal mucosa and swept toward the pharynx by the cilia. Mucous is supplied to the nasal epithelium by glands and goblet cells within the mucosa.

There is a cyclic variation in the flow resistance of each nasal passage (*6, 7*) which is due to the regular constriction and dilation of the mucosal venous cavernous tissue (*8*) and is thought to hypothalamically regulated (*9*) via the Vidian nerve (*10*). At the peak of the cycle, one nasal cavity has low flow resistance and the mucosa is moist while the other has high flow resistance and dry nasal mucosa (*11*).

***Olfactory Epithelium.*** The human olfactory epithelium, located at the apex of the nasal cavities (Figs. 1 and 2), encompasses about 2-4 $cm^2$ and contains about $10 \times 10^6$ receptor cells (*12*). It is covered by a mucous layer secreted by Bowman's gland.

The olfactory epithelium (Fig. 3) is composed of

* United States Environmental Protection Agency, Neurotoxicology Division, Neurophysiology Branch and University of North Carolina, Psychology Department, Chapel Hill, North Carolina 27514.

† Send reprint requests to: Vernon A. Benignus, Environmental Protection Agency/MD-58, Medical Research Building C-224H, University of North Carolina, Chapel Hill, N. C. 27514.

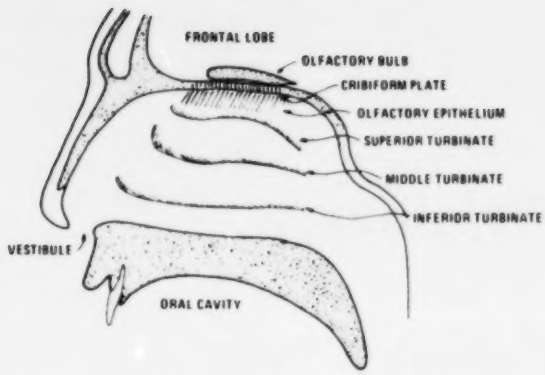


FIGURE 1. Midsagittal view of nasal cavity, showing location of olfactory structures and turbinates. Adapted from Proetz (*2*).

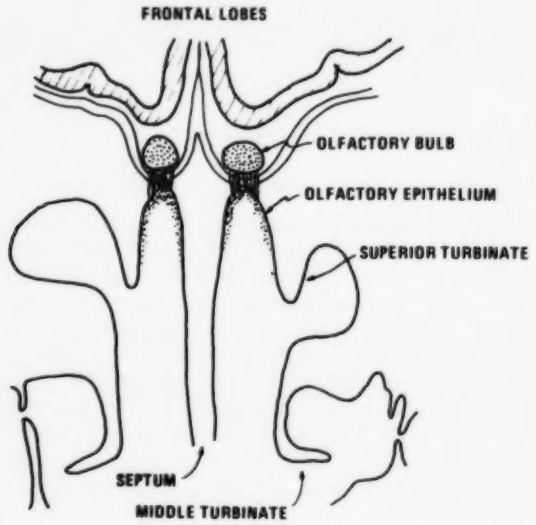


FIGURE 2. Frontal section through nasal cavity showing the location of olfactory structures with respect to the brain. The convoluted shape of the turbinate bones is also shown. Adapted from Schneider (*3*).

receptor cells, basal cells and sustentacular cells. The receptors are bipolar sensory cells and are often compared morphologically and functionally to the bipolar retinal cells. They are capped by immotile cilia that extend about 160μm into the mucous. It is presumed that the receptor sites are located in the cilia (*13*). Unmyelinated axons of receptors

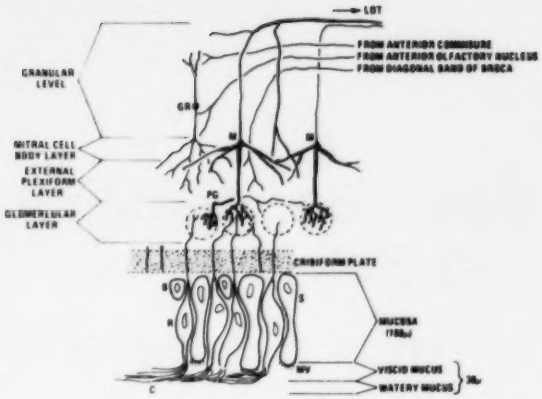


FIGURE 3. Cells and connections of the olfactory epithelium and olfactory bulb: (B) basal cell; (C) olfactory cilia; (GR) granular cell; (M) mitral cell; (PG) periglomerular cell; (S) sustentacular cell; (mc) microvilli.

extend through the cribriform plate (a perforated area of the ethmoid bone) and synapse within the olfactory bulb (OB). There is a loose topographic mapping from the olfactory epithelium to the olfactory bulb.

The sustentacular cells, as the name implies, support the receptor cells and provide a secretion with an unknown role and composition (*12*, *14*, *15*). Also located in the olfactory epithelium are basal cells whose function is not known.

***Trigeminal Innervation.*** The non-olfactory nasal cavity is innervated by free nerve endings of the ethmoid branch of the trigeminal nerve (*16*). These endings are found in the epithelium of the pharynx as well. The trigeminal nerve synapses in the trigeminal nucleus in the pons.

## Central Olfactory Structures

The connections and ultrastructure of the olfactory sense in the central nervous system (CNS) have been recently reviewed by Shepherd (*17*, *18*). Other reviews (*19-21*) provide background information.

***Olfactory Bulb.*** Major connections of the olfactory bulb (OB) are shown in Figure 3. Axons of receptor cells synapse in glomeruli (spherical areas of dense neuropil) on mitral and periglomerular cells. About 25,000 receptor axons synapse in each glomerulus with 25 mitral cells (a 1,000:1 convergence ratio). Axons of mitral cells form the lateral olfactory tract (LOT) and carry impulses toward

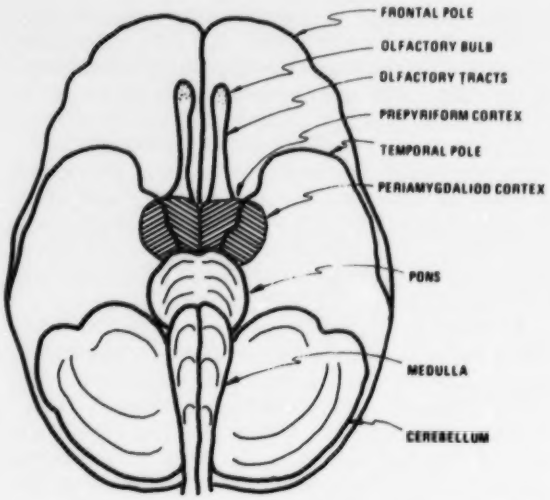


FIGURE 4. Ventral view of the human brain. Cross-hatched areas show approximate area of termination of primary olfactory fibers. Structures to which synapses are made underlie these areas.

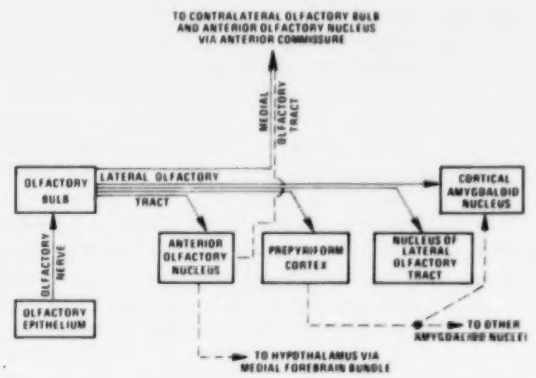


FIGURE 5. Schematic of principal centripetal connections of the olfactory bulb.

the CNS. Axon collaterals of mitral cells also make connection to other cells within the bulb. Periglomerular cells, which outnumber mitral cells about 20:1, make horizontal connections between glomeruli.

Granular cells, in deeper layers of the olfactory bulb, make dendrodendritic connections with mitral cells and with each other as well as axodendritic connections with centrifugal neurons. Centrifugal neurons synapse mainly with the granule cells and originate in the contralateral olfactory bulb (crossing via the anterior commisure), in the ipsilateral anterior olfactory nucleus and in the ipsilateral diagonal band of Broca. The latter centrifugal fibers extend to synapse with periglomerular cells.

***Olfactory Cortex.*** A simplified ventral view of the human brain in Figure 4 shows the approximate area of olfactory fiber termination. Principal centripetal cortical connections are shown schematically in Figure 5. The lateral olfactory tract courses ventrally over the prepyriform cortex toward the amygdaloid body and along its course fibers branch from it and spread across the cortical ventral surface to synapse in the anterior olfactory nucleus, the prepyriform cortex, the nucleus of the lateral olfactory tract and the cortical amygdaloid nucleus. Mitral cell axons from the lateral olfactory tract form axodendritic synapses with pyramidal cells in the outer molecular layer of the cortex but do not reach deeper layers.

Olfactory cortex structures send secondary fibers (which have made synaptic connections with mitral cell axons) to other CNS sites. The anterior olfactory nucleus contributes fibers to the medial forebrain bundle which terminates in the hypothalamus as well as sending centrifugal fibers to the granule cells of the ipsilateral olfactory bulb. Prepyriform cortical fibers are traceable to the amygdala, the hypothalamus and possibly the hippocampus. Amygdala cells fibers send send axons to the hypothalamus, the prepyriform cortex and the hippocampus. This is, of course, not an exhaustive list of secondary fiber connections. Only major connections are noted.

Other multisynaptic CNS olfactory connections have recently been reported (*22-24*). These involve pathways originating in the amygdala and prepyriform cortex, passing through the thalamus and terminating in the orbitofrontal cortex. This represents a neocortical site as opposed to the more classical allocortical (old cortex) and limbic projections.

## Physiology and Function

### Psychophysiology

An olfactory stimulus consists of airborne chemical molecules within the molecular weight range of approximately 15 to 300. The intensity of the stimulus is a function of the number of molecules of odorous substance in contact with the olfactory epithelium. The rate of perceived increase in intensity with increased odorant concentration is not constant across different odorants but is a log function of concentration with the slope being influenced by water solubility of the odorant (*25*) and chemical functional groups (*26*).

Threshold, usually defined as the stimulus concentration the subject detects 50% of the time, is

somewhat more difficult to study. The problem of adaptation (reduced sensitivity) to the stimulus can occur with multiple presentations of the same stimulus. Cross-adaptation may also occur with successive presentations of different stimuli. Measurement of thresholds presents the additional problems of individual variability and technique (*27*), with practice (*28*) and with instrumentation (*29*).

The classification of odor quality has been a puzzle for centuries (*30*). Numerous theories have been created to explain olfactory quality (*31*). Amoore (*32*) postulated and Beets (*33*) elaborated upon a stereochemical theory of olfaction based upon receptor sites on the cilia. These hypothesized sites had different shapes to receive complimentarily shaped primary odor molecules. Their hypothesized primary odors were deduced from organic chemistry literature and were analogous to primary colors in vision. Unfortunately, evidence for such receptor sites and primary odors is poor; correlations with actual perceived odor qualities are far from perfect, and there are notable exceptions to their rules.

Davies (*34*) proposed a puncture and penetration theory of olfaction whereby the odorant molecules actually enter the receptor cell and precipitate depolarization. Odor quality was hypothesized to be determined partly by the rate of diffusion through the membrane and the resistance of the individual receptor membranes to puncturing. There is no evidence that odorant molecules actually penetrate a receptor or that they have different diffusion rates.

Wright (*35*) proposed a molecular vibration theory of odor quality. In this theory, the vibrational frequency of molecules in the far-infrared determines the quality, while volatility, adsorbability and water–lipid solubility determine the potency of the odor. This idea has been widely criticized (*31*, *36*, *37*).

A spatio-temporal model of olfaction has been proposed (*38*). In this chromatographic analogy, the pattern of spread of odorant molecules across the olfactory epithelium determines olfactory quality. There is little solid evidence for support of this new theory.

In summary, while there are many theories about olfaction, most seem not to provide hard evidence in their favor. While most involve the structure of the molecule, it is not clear what physicochemical attribute of molecules makes them odiferous. The unknown nature of the receptor mechanism further complicates the problem.

## CNS Olfactory System

***Olfactory Bulb.*** The anatomy of the olfactory bulb suggests that this structure is more than a simple "telephone repeater" station. At the glomerular level, sensory cells fire into a synaptic neuropil of mitral and periglomerular cell dendrites. Since mitral cells are the principal neurons in the olfactory bulb, their apparent function is transmission of sensory data. Even at the glomerular level, however, there is considerable data processing because of the network of periglomerular cells. There appears to be odor specificity at the glomerular level (*39*, *40*), and, because of inhibitory synaptic processes, there is considerable spatial and temporal sharpening of input data (*41*, *42*).

As seen in Figure 3, connections in the inner three layers of the olfactory bulb deal with interactions of sensory input data and output from the CNS. These interactions occur in synapses between mitral and granule cells with axons from centrifugal cells. Periglomerular cells also receive centrifugal influence. It has been demonstrated that the synaptic connections in the inner layers of the olfactory bulb form recurrent inhibitory loops (*43-45*) which are responsible for the generation of the oscillatory electroencephalogram (EEG) which can be measured with macroelectrodes in the olfactory bulb (*46*). The inner layers of the olfactory bulb, therefore, seem to integrate sensory stimuli with centrifugal impulses and thus perform higher level data processing to aid in olfactory perception and control of olfactory-guided behavior.

***Odor Code.*** The question of how odor information is coded and transmitted to the brain is largely unanswered. There are several lines of evidence, but the basic problems with all of them are that salient stimulus dimensions are not understood and, perhaps as a consequence of these problems, correlations of electrophysiological responses with stimulus properties are rather low, even though statistically significant.

There is mounting evidence for an odor specificity in the mitral cells of the olfactory bulb (*39*, *40*, *47*) which might be ascribable to spatially organized projections from the olfactory epithelium (*48-50*). Some evidence for olfactory coding in olfactory bulb EEG has also been reported (*51*). In both the EEG and single unit response data, however, it has been shown that the putative codes also are influenced by habituation and learning (*52-55*).

Variations in the meaning of odorants to the organism and the effects of arousal states of the organism can easily be confused for odor codes unless these variables are controlled. Similarly, unless intensity of stimulation is controlled for various odors, the code for intensity might be mistaken for an odor code. While the cited research provides suggestions for further work, there were many uncontrolled variables in these studies and results

contained high residual variance. At this time no firm groundwork has been laid to aid theorists in disentangling pure sensory information from processed and interpreted data. Perhaps the CNS multiplexes these data and generates signals in which interpretational modifiers are appended to sensory data "words."

***Brain Olfactory Mechanisms.*** The structures in the brain which receive olfactory input data are also known to be involved in the regulation of basic behaviors which are well reviewed by Thompson (*56*). Laboratory animals will work to receive electrical stimulation to the medial forebrain bundle. The hypothalamus is intimately involved in the regulation of hunger, thirst, sexual activity and sleep. Lesions in the amygdala and surrounding structures produce alterations in sexual and social behaviors. All of these areas receive impulses from the olfactory bulb, and, indeed, the electrical activity of these centers is sometimes almost completely dominated by such inputs. It is not clear how much of the information transmitted to these CNS centers is sensory data and how much of it has been processed into signals for action. Whatever the nature of the signals which are sent to the CNS, the signals are sent to widespread and important sites. There are recent data indicating that the human amygdala EEG correlates somewhat with odor qualities (*57*).

## Behavior

For neurotoxicologists, the importance of anatomy and physiology rests upon the consequences of disturbances in the CNS on behavior. Behavior is the final common pathway. In nonhuman species it is well known that olfactory stimulation can very strongly influence sexual behavior (*58*, *59*) as well as social behaviors between and within species, such as aggression, territorial defense and identification (*60*, *61*). It is usually assumed, however, that olfactory stimuli play only minor roles in influencing the behavior of humans. This assumption is based largely upon introspection about the causes of behavior rather than empirical evidence. In the case where sensory information is distributed to limbic system centers, however, it is questionable whether introspection would yield any information. Such subcortical input might in fact exert so-called "unconscious" influence. If this is the case, influences of odor on human behavior could be quite important, especially because of their unobtrusive nature. With all of the attempts in our society at control of the olfactory environment, by means, e.g., of perfumes and deodorants, and with all of the odiferous environmental pollution, it seems especially important to understand the effects of odors upon humans.

Evidence is beginning to emerge on the role of the olfactory sense on human behavior. Humans can use odors to identify individuals (*62*, *63*) although it is unknown to what extent they normally do so. Humans generate pheromonelike compounds (*64*, *65*), and such pheromones affect sexual attractiveness in both males and females (*66*, *67*). Other social behaviors, in addition to sexual attraction, might well be affected by odor cues (*68*). There are correlations between olfactory acuity in women and menstrual variations (*69*, *70*). There is also evidence that the smell of jasmine flowers inhibits lactation in human females (*71*).

While the findings regarding olfactory effects on human behavior are only suggestive, it is certainly logical on anatomical and physiological grounds that such effects should exist since olfactory connections are made to widespread and important CNS sites (*72*). To assume that the effects are not important might be to overlook a strong and yet unobtrusive effect of the olfactory environment on everyday human behavior. More research on this issue is required.

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